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REVIEW ARTICLE

Inherited ichthyosis: Syndromic forms

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ABSTRACT

Among diseases that cause ichthyosis as one of the symptoms, there are some diseases that induce abnormalities in organs other than the skin. Of these, diseases with characteristic signs are regarded as syndromes. Although these syndromes are very rare, Netherton syndrome, Sjögren–Larsson syndrome, Conradi–Hünermann–Happle syndrome, Dorfman–Chanarin syndrome, ichthyosis follicularis, atrichia and photophobia (IFAP) syndrome, and Refsum syndrome have been described in texts as representative ones. It is important to know the molecular genetics and pathomechanisms in order to establish an effective therapy and beneficial genetic counseling including a prenatal diagnosis.

Key words: genetic disease with ichthyosis, ichthyosis, multisystem defects, organ systems other than skin.

INTRODUCTION

The ichythyoses consist of clinically and genetically heterogeneous Mendelian disorders of cornification.[1] Inherited ichthyoses are subdivided into non-syndromic ichthyoses and syndromic ichthyoses. Non-sydromic ichthyoses have phenotypes that are only seen in skin. In contrast, syndromic ichthyoses have phenotypes due to underlying genetic defects are seen not only in skin but also in other organs.[2]

NETHERTON SYNDROME (ONLINE MENDELIAN INHERITANCE IN MAN [OMIM] NO. 256500)

Epidemiology

Netherton syndrome is rare. Its incidence is higher in females. In Japan, more than 10 patients have been reported. Its incidence is reportedly approximately 1/200 000 neonates. Since this syndrome was reported by Netherton in 1958, 43 case reports have been published (English language), including the latest one presented by Smith *et al.* in 1995.[3] Eighteen percent of congenital erythrodermas are thought to be due to Netherton syndrome.[4]

Etiology/pathological physiology

Netherton syndrome is an autosomal recessive inheritance-related disease. A causative gene is a serine protease inhibitor, lympho-epithelial Kazal-type-related inhibitor (LEKTI). This gene has been shown to code a serine protease inhibitor, Kazal-type 5 (*SPINK5*). The *SPINK5* gene is present on chromosome 5q32. LEKTI is the first serine protease inhibitor to be shown to be involved in dermal cornification disorder and hair dysplasia. Considering that the *cathepsin C* gene causes Papillon–Lèfevre syndrome, proteolysis may be closely involved in the formation of the epidermis and the differentiation of keratinocytes.

In the skin of patients with Netherton syndrome, thinning of the granular layer and stratum corneum is observed. This reflects that the mutation of *SPINK5* genes affects skin barrier formation. In patients with Netherton syndrome, infection or dermal inflammation is repeated. This phenomenon is associated with abnormalities in the stratum corneum, but abnormalities in the maturation process of T cells may be involved in repeated infection/dermal inflammation and an atopic predisposition (an increase in the blood immunoglobulin [Ig]E level), considering the expression of LEKTI protein in the thymic epithelium. Barrier dysfunction is also pointed out.[4]

Clinical symptoms

Netherton syndrome is characterized by three main signs: (i) ichthyosis linearis circumflexa (ILC) or congenital ichthyosis, such as congenital ichthyosiform erythroderma (CIE); (ii) bamboo hair; and (iii) atopic predisposition. In 1958, Netherton presented a syndrome that causes red exanthema with generalized exfoliation, bamboo hair and an atopic predisposition as primary symptoms, and reported it as "a unique case of trichorrhexis nodosa: bamboo hair".[5] Thereafter, Wilkinson *et al.*[6] reported a patient with ILC, bamboo hair and an atopic predisposition, and called this condition Netherton syndrome.

Typical patients show scale-attached erythroderma at the time of birth. Collodion babies are rarely born. Symptoms of ILC appear at the time of birth or early after birth: systemic CIE involving the trunk and limbs, atopic dermatitis-like diffuse erythema and scales. In these patients, erythema is sometimes symmetrical, showing various shapes, such as tortuous and map-like shapes. It shows efferent enlargement and dike-like protrusion at the margin. As scales and crusts are attached to the protrusion site, it is termed double-edged scale. In some cases, lichenification of the elbows and knees is observed.

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Hair abnormalities are specific to this disease. All hairs are affected. Hair is short, sparse, dry and not lustrous. Under a light microscope, nodes are observed (trichorrhexis invaginata/nodular trichorrhexis, the distal area of hair invaginates toward its proximal area). However, this finding appears later, and the severity differs among patients. Eyelash or eyebrow defects are observed in some cases.

An atopic predisposition appears in most patients with Netherton syndrome. Chronic hives, bronchial asthma, allergic rhinitis, hay fever, an increase in the serum IgE level and eosinophilia have been reported as symptoms. As other symptoms, growth disorder, recurrent infection, aminoaciduria, a low IQ (mental disorder), mental retardation, epilepsy-like attacks and pruritus have been indicated.

Histopathological findings

There are no characteristic findings in erythema or scale-attached sites, and psoriasis-like changes (elongation of the epidermal ridge, overcornification and incomplete cornification) are noted. On transmission electron microscopy, immature lamellar granules are observed between keratinocytes. Briefly, the lamellar granule laminar structure is not formed, and is substituted for a substance with a high electron density. Furthermore, the double lipid structure of the keratinocyte membrane is destroyed through the deposition of the high-electron-density substance. In keratinocytes, a large number of fatty droplets are present. Furthermore, nuclei remain, and a large number of inclusion bodies are observed. At the double-edged scale site, intracellular edema is observed in spinous stratum cells. Some areas show spongiosis. Some patients show multilocular blebs or micropustules in keratinocytes. Others show the deposition of uniform, periodic acid-Schiff-positive, diastase-resistant substances, which may be derived from serum, in keratinocytes with incomplete cornification. In the site of trichorrhexis invaginata (bamboo hair), the distal area of hair invaginates like a bulb toward its proximal area (calix). This may be related to insufficient cornification of the hair cortex. On transmission electron microscopy, a large number of high-electron-density deposits are observed in the hair cuticle area.

Examination finding

Pathological examination

It must be confirmed whether or not the findings described above are observed. For differential diagnosis, the diseases presented in the following section "diagnosis/differential diagnosis" should be considered.

Immunological/biochemical tests

An increase in the number of leukocytes (especially eosinophils) in peripheral blood, a high serum IgE level and a low IgM level are observed. A study reported that, among urinary amino acids, there were increases in the levels of glycine, histidine and serine.

Diagnosis/differential diagnosis

It is not difficult to diagnose this syndrome based on characteristic clinical findings. In particular, attention should be paid to characteristic abnormalities of hair.

This syndrome should be differentiated from psoriatic erythroderma, Darier's erythema annulare centrifugum, subcorneal pustular dermatosis, Wiskott–Aldrich syndrome, non-bleb-type congenital ichthyosiform erythroderma, and ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature (IBIDS).

Treatment

During the neonatal period, water and electrolyte management must be strictly conducted. According to a study, patients responded to ammonium lactate lotion, the p.o. administration of retinoid and psoralen plus ultraviolet A therapy (PUVA) therapy.

Course/prognosis

The prognosis of some patients with recurrent infection is unfavorable (death during infancy).

SJÖGREN–LARSSON SYNDROME (OMIM NO. 270200)

Epidemiology

Sjögren–Larsson syndrome (SLS) is rare, and there is no sex difference in its incidence. Although the exact incidence is unclear, Jagell *et al.*[7] reported that the incidence in Sweden was 0.6/100 000 persons between 1901 and 1977. In Japan, 62 patients have been reported since the first patient was presented by Kakinuma *et al.* in 1967.[8]

Etiology/pathological physiology

Sjögren–Larsson syndrome is an autosomal recessive inheritance-related disease.[9] A study reported that fatty aldehyde dehydrogenase (FALDH) activity was reduced in fibroblasts cultured from the skin of patients with SLS. FALDH is localized in microsomes, and is an enzyme essential for oxidizing long-chain fatty aldehyde to fatty acids. On the other hand, genetic linkage analysis showed that the gene involved in SLS was present on chromosome 17p11.2. De Laurenzi *et al.* performed cloning of the cDNA of human FALDH, and indicated that this gene was present on chromosome 17p11.2. In addition, they conducted sequencing of mRNA and genomic DNA extracted from fibroblasts, which had been cultured from the skin of SLS patients, to identify homo- and heterozygous mutations.[10]

It has been shown that SLS is associated with FALDH gene mutations. The FALDH gene consists of 11 exons, measuring approximately 30 kb in length. (However, its main transcriptional product is a protein consisting of 485 amino acids [10 exons]. A protein consisting of 508 amino acids [11 exons] is synthesized through alternative splicing.) FALDH gene mutations irregularly occur. The tissue deposition of fatty alcohol, fatty aldehyde and other lipid metabolism products related to a reduction in FALDH activity may be involved in the pathogenesis of SLS.

Clinical symptoms

In 1956, Sjögren (Sweden) reported five patients with congenital ichthyosis, spastic paralysis of the limbs and mental weakness as three main signs. In 1957, he presented 28 patients in

cooperation with Larsson.[10] Since then, patients have been accumulated, and such a condition with similar signs has been regarded as SLS. Primary symptoms include spastic paralysis of the limbs (particularly marked in the lower limbs), mental retardation and congenital ichthyosiform exanthema. Mental retardation is relatively severe, and more than 50% of patients show an IQ of 50 or lower. In most patients, mental developmental retardation is detected during childhood. Spastic paralysis is marked in the lower limbs, being symmetrical. Gait disorder is often observed. Convulsion is noted in approximately 40% of patients.

Most patients show exanthema at the time of birth, and it becomes typical before 1 year of age. In Europe and the USA, many investigators have reported such exanthema as foliaceus ichthyosis or congenital ichthyosiform erythroderma. In Japan, it has been presented as acanthosis nigricans-like exanthema in many case reports. These types of exanthema are marked in the cervix/abdomen and on the flexion side of the limbs. The incidence of exanthema of the face and palms/heels is relatively low. In particular, it is more marked in the friction site. At the time of birth, the collodion film is not formed. Exanthema is brown or beige. In some cases, erythema is observed at the margin. When the site of exanthema is rubbed, furfuraceous desquamation is observed. Photo luminescent freckles or pigmental degeneration of the fundus retina, ventricular enlargement and cerebral atrophy have also been indicated. Scoliosis is observed in some cases.

Histopathological findings

The skin of SLS patients shows the histology of ichthyosis. Hyperkeratosis, papillomatosis, incomplete cornification, epidermal thickening and thickening of the granular layer are observed. Changes in the Golgi system and an increase in the number of mitochondria on electron microscopy have been reported. Furthermore, an abnormal disk-like substance is present between keratinocytes according to a study.

Examination finding

Neurological test

In patients with SLS, spastic paralysis of the limbs is observed. A study reported that computed tomography (CT) revealed hypodensity of the white matter.[11] Abnormalities in the white matter on magnetic resonance imaging (MRI) have also been reported.

Biochemical test

As FALDH comprises fatty alcohol:NAD^+ oxidoreductase (FAO), a definitive diagnosis is made by measuring FALDH or FAO activities. Fibroblasts are cultured from the patient's skin, and the activities of the above enzymes are measured using them. Recently, gene analysis-based test methods have been developed: a method in which restriction endonuclease cleavage of gene segments amplified by polymerase chain reaction (PCR) is conducted, and a method in which allele-specific PCR is applied. However, genetic diagnosis is expensive, and enzymatic diagnostic methods to measure FALDH or FAO activities may be primarily adopted for the time being. Rizzo *et al.* analyzed fatty acids in scales from patients with SLS using gas chromatography, and reported that the levels of free fatty acids were significantly higher than in normal skin scales.[9]

Enzyme histochemical method

Judge *et al.*[12] reported an enzyme histochemical method using frozen skin sections. However, some patients did not show any abnormalities when this method was used.[13] This reflects the fact that the etiology of SLS varies.

Diagnosis/differential diagnosis

Sjögren–Larsson syndrome must be differentiated from Refsum syndrome, and non-bleb-type congenital ichthyosiform erythroderma. In patients with Rud syndrome, various endocrinological abnormalities are noted, and spastic paralysis is observed in patients with SLS, but not in those with Rud syndrome. On this basis, a differential diagnosis should be made. A patient in whom FAO activity was normal despite the same clinical symptoms as SLS was reported.

Treatment

Skin-softening drugs, keratolytic drugs and topical vitamin D_3 preparations should be applied. According to a study, the p.o. administration of retinoid is effective. To treat skeletal deformities of the limbs, muscular atrophy and contracture, orthopedic surgery is performed. Hooft *et al.* and Takayama *et al.* reported patients in whom the administration of medium-chain fatty acids reduced intestinal symptoms and exanthema.[14,15]

Course/prognosis

Most patients die of respiratory diseases. The average life span is reportedly 22 years (male, 15 years; female, 26 years).

REFSUM SYNDROME (OMIM NO. 266500)

Epidemiology

Refsum syndrome is a congenital metabolic disease that was initially reported as heredopathia atactica polyneuritiformis by a neurologist, Sigvald Refsum (Norway), in 1946.[16] From then until 1975, only 73 patients were reported globally.[17] This syndrome is very rare, and no patients have been reported in Japan.

Etiology/pathological physiology

Refsum syndrome is an autosomal recessive inheritance-related disease.[18] The accumulation of a branched fatty acid, phytanic acid (3,7,11,15-tetramethylhexadecanoic acid), in systemic organs (particularly adipose tissue, kidney, liver and myelin sheath) may be involved in the pathogenesis of this disease. Klenk and Kahlke indicated that the blood and tissue levels of phytanic acid were increased.[19] The mutation of a gene coding phytanoyl-CoA hydroxylase (PHYH) (this gene has been shown to be located on chromosome 10p13; the *PHYH* gene measures 21 kb in length, consisting of nine exons and eight introns) may increase the phytanic acid level.[20]

To date, mutations, such as R275W, the deletion of codon 46–82, base 164T deletion (164delT), N269H and insertion of 3 bp (GCC) immediately after base 576 (576-577insGCC), have been identified (R, arginine; W, tryptophan; N, asparagine; H, histidine). Furthermore, the mutation of a gene coding peroxisomal α-methylacyl-CoA racemase has been detected in some patients. The results of genetic linkage analysis showed that there was a family in which the causative gene was not present on chromosome 10p13, although clinical findings suggested Refsum syndrome. In this family, genes other than the above two genes may be etiologically involved.

Clinical symptoms

Refsum syndrome develops during childhood to adolescence. Most patients show a progressive course, but remission and exacerbation are repeated in some patients. Four of its signs are pigmentous retinitis, peripheral neuritis, cerebellar ataxia and an increase in the cerebrospinal fluid level of protein. In addition, symptoms, such as anosmia, hemeralopia, vision disorder, cataract, muscular atrophy, cardiomyopathy, bone disorder, progressive myelin degeneration, functional disorder of the nervous system, cochlear hearing loss, ichthyosis and renal failure, are observed. The skin is dry and cornification is marked, with furfuraceous desquamation. Most scales are brown. Especially in the trunk, cornification is marked. Furthermore, hyperkeratosis is also marked at the olecranon and patella. Dermal symptoms are marked during childhood and adolescence.

Histopathological findings

Thickening of the stratum corneum is observed, and the number of cells in the granular layer is decreased. In some cases, small vacuoles are present in cells in the basal layer of the epidermis. On electron microscopy, lipid droplets are detected in the cytoplasm of basal cells.

Examination

Neurological examination

Electroencephalography, intelligence tests, CT, MRI and X ray are performed. Infantilism or microcephaly is observed in some patients. Chronic progressive polyneuropathy is noted. This is associated with distal lower-limb-predominant muscular atrophy and muscular weakness. As cerebellar symptoms, ataxic gait, intention tremor and nystagmus are observed. The motor/sensory nerve conduction velocity is reduced.

Ocular symptoms

Pigmental degeneration of the retina and hemeralopia frequently occur. Concentric contraction of the visual field gradually appears. Cataract and corneal opacity are also observed.

Biochemical test

It is necessary to verify the presence of phytanic acid in plasma lipid fractions using gas chromatography.

Cerebrospinal fluid test

In all patients, there is an increase in the protein level, but there is no increase in the cell count.

Diagnosis/differential diagnosis

Refsum syndrome must be differentiated from SLS, Rud syndrome and IBIDS. In patients with SLS, FALDH or FAO activities in fibroblasts cultured from the skin are low, facilitating differentiation. In those with Rud syndrome, hypogonadism is present. In those with IBIDS, there is a decrease in the sulfur content of hair.

Treatment

Phytanic acid detected in plasma in the presence of this disease is derived from dietary phytol and phytanic acid. Therefore, the consumption of butter, tuna, cheese, lamb, beef tallow and vegetables, which contain a high level of these substances, should be restricted (daily phytanic acid intake should be limited to ≤10 mg). A study reported that plasmapheresis was effective. To treat dermal lesions, topical therapy for ichthyosis should be conducted.

Course/prognosis

According to a study, survival of 34 years after making a definitive diagnosis was achieved by the ingestion of a phytanic acid-restricted diet. However, the clinical course varies among patients; a patient died of cerebral hemorrhage after 5 years despite the ingestion of a phytanic acid-restricted diet.

Reference

In addition to classical Refsum syndrome, infantile Refsum syndrome related to peroxisome biogenesis factor (PEX)-1 or -2 gene mutations and Refsum disease with increased pipecolic acidemia, for which the causative gene remains to be clarified, occur.

MULTIPLE SULFATASE DEFICIENCY ICHTHYOSIS (OMIM NO. 272200)

Epidemiology

Multiple sulfatase deficiency (MSD) is rare. Since Austin reported this disease in 1965, 50 or fewer patients were reported before 1997.[21,22]

Etiology/pathological physiology

Cholesterol sulfate plays an important role in the adhesion of keratinocytes in the substratum corneum. It exists as a cell membrane component of keratinocytes, and is negatively charged, attracting calcium ions and leading to the calcium-mediated adhesion of keratinocytes. Steroid sulfatase (STS) separates the sulfate group from cholesterol sulfate in the stratum corneum. As a result, keratinocytes gradually dissociate/deciduate toward the superior layer. In patients with MSD, STS activity is disordered.[23]

Patients with X-linked ichthyosis also show STS abnormalities. In those with MSD, at least seven sulfatases are simultaneously affected. However, the chromosomal positions of

genes coding these sulfatases differ. As STS activity is secondarily deleted in those with MSD, exfoliation of the stratum corneum is delayed, leading to overcornification. In arylsulfatase A (ASA) from MSD patients, there is no conversion of Cys-69 to 2-amino-3-oxopropionic acid. This may induce a reduction in sulfatase activity (or no activity), resulting in ichthyosis related to MSD.

Multiple sulfatase deficiency is caused by homozygous or compound heterozygous mutation in the sulfatase-modifying factor-1 (*SUMF1*) gene.[23]

Clinical symptoms

Patients show symptoms related to the concomitant development of three disease groups: metachromatic leukodystrophy with the deposition of sulfatide in the nerve tissue or kidney, resulting from abnormalities in ASA, acidic mucopolysaccharidosis with the accumulation of heparan sulfate or dermatan sulfate in a large number of cells, including fibroblasts, resulting from abnormalities in arylsulfatase B, and ichthyosis related to STS abnormalities. At 2 or 3 years of age, patients become unable to sit, and speech development is retarded in comparison with that of healthy children. In addition, incontinence is observed. Patients also show symptoms of blindness and speech impairment. Their faces develop a specific appearance, and hepatosplenomegaly, delayed growth, muscular abnormalities, corneal opacity, convulsion and hydrocephalus are observed. Most patients die at 10–15 years of age.

Ichthyosis is observed from 2 or 3 years of age. Dermal symptoms are severer than in ichthyosis vulgaris. Large, dark brown, leaf-like scales are characteristic. The symptoms are more marked on the extensor surfaces of the limbs. The scalp, cervix, anterior ears and abdomen may be affected. Neither the palms nor the heels are affected.

Histopathological findings

Histopathologically, thickening of the stratum corneum and slight thickening of the granular layer occurs.

Examination

Urinalysis

Urinary mucopolysaccharides are quantified. An increase in the uronic acid level is observed.

Sulfatase activity test

Sulfatase activity is measured using lymphocytes from patients or fibroblasts collected from the patient's skin and cultured.

Ophthalmological examination

Pigmental degeneration of the retina and corneal opacity are observed in some patients.

Neurological examination

The nerve conduction velocity is measured, and sural nerve biopsy is performed. Cerebral CT and MRI are conducted.

A definitive diagnosis is made based on the results of a sulfatase activity test.

Treatment

Currently, it is impossible to stop the progression of metachromatic leukodystrophy and acidic mucopolysaccharidosis. Treatment consists of nursing and therapies for complications. A study indicated that a γ-aminobutyric acid-aminotransferase inhibitor, vigabatrin, was effective for neurological symptoms in children with metachromatic leukodystrophy. Enzyme replacement therapy, involving the i.v. injection of normal enzymes, is not successful. Recently, bone marrow transplantation has been selected. To treat ichthyosis, skin-softening drugs, keratolytic drugs and topical vitamin D_3 preparations should be applied.

Course/prognosis

Most patients die at 10–19 years of age.

KERATITIS–ICHTHYOSIS–DEAFNESS SYNDROME (OMIM NO. 148210)

Epidemiology

Keratitis–ichthyosis–deafness (KID) syndrome is rare. Since Burns reported it in 1915, 60 patients had been reported in the English-language published work before 1996.[24,25]

Etiology/pathological physiology

Keratitis–ichthyosis–deafness syndrome is considered to be an autosomal dominant inheritance-related disease.[26] In 1981, Skinner *et al.* termed a syndrome characterized by keratitis with corneal neovascularization, overcornification of the skin, and sensory nerve-related hearing disorder, KID syndrome. KID syndrome is caused by heterozygous mutation in the connexin-26 gene, *GJB2*.[26] *GJB2* gene is located at human chromosome 13q12.11.

Clinical symptoms

Although the term KID syndrome is generally known, it does not always reflect the clinical features of the skin. Dermal lesions comprise papilloma-like overcornification, but not ichthyosis exanthema. Neither eyelashes nor eyebrows are dense. Progressive alopecia of the scalp is noted. The skin at the lesion site is characteristic. Fine particulate substances seem to be attached, and a spike-like morphology is often observed. This finding is particularly marked in the palms and soles. Nail deformities are often observed. In the oral cavity, leukoderma keratosis, erythematous lesions and dental abnormalities are often noted. A study reported that spinocellular carcinoma developed from dermal or lingual lesions. Fungal infection often occurs concomitantly. Keratitis and hearing disorder are present.

Pathological findings

The epidermis is denticulate. At the lesion site, thickening of the stratum corneum is present. Follicular plugging is noted. On electron microscopy, there are no marked abnormalities. However, several studies indicated glycogen storage in various tissues.

Examination

Hearing test
Audiography is performed to investigate the presence or absence of hearing disorder.

Ophthalmological examination
Keratitis, photophobia and low vision appear during childhood. Bilateral pannus is observed.

Diagnosis/differential diagnosis

Keratitis–ichthyosis–deafness syndrome must be differentiated from ichthyosis hystrix Curth–Macklin, ichthyosis hystrix Curth–Macklin syndrome with deafness, and congenital erythrokeratoderma. In patients with ichthyosis hystrix Curth–Macklin, the intermediate filaments of keratin surrounding a nucleus like a shell are detected on electron microscopy. In those with ichthyosis hystrix Curth–Macklin syndrome with deafness, there is a marked decrease in the number of the intermediate filaments of keratin on electron microscopy. Congenital erythrokeratoderma does not cause keratitis. Considering these characteristics, a differential diagnosis should be made.

Treatment

A study reported that retinoid therapy was effective. The application of keratolytic drugs is also selected. For hearing disorder control, hearing aids and cochlear implants are used. If malignant tumors of the skin develop, surgery should be performed.

Course/prognosis

The prognosis is favorable, but exanthema may persist over the lifetime. Malignant neoplasms arose in some cases.

CONGENITAL HEMIDYSPLASIA, ICHTHYOSIFORM ERYTHRODERMA OR NEVUS AND LIMB DEFECTS SYNDROME (OMIM NO. 308050)

Epidemiology

Congenital hemidysplasia, ichthyosiform erythroderma or nevus and limb defects (CHILD) syndrome is extremely rare. Since Zellweger and Uehlinger reported it in 1948, 30 patients had been reported in Europe and the USA before the report published by Hashimoto *et al.* in 1995.[27,28] In Japan, four patients have been reported. They consisted of three females and one male. In males, this syndrome is considered to be fatal. Concerning the affected side, there is no laterality.

Etiology/pathological physiology

With respect to hereditary forms, X-linked recessive or dominant inheritance has been reported. However, many investigators support X-linked dominant inheritance (X-linked dominant male lethal). König *et al.*[29] identified NSDHL gene (3β-hydroxysteroid dehydrogenase) mutations. NSDHL (NAD [P]H steroid dehydrogenase-like) protein is an enzyme involved in the process of cholesterol synthesis. A105V and G205S missense mutations in NSDHL molecules, as well as Q210X and R88X nonsense mutations, have been identified (A, alanine; V, valine; G, glycine; S, serine). The relationship between clinical features and the type of mutation remains to be clarified.

Clinical symptoms

In most patients, dermal symptoms are present at the time of birth. However, they appear within a few weeks after birth in some patients. On the unilateral skin, ichthyosiform erythroderma is observed. Although this symptom is irreversible, it is reduced with growth in some patients. The exacerbation and remission of exanthema are sometimes repeated. Limb reduction/defects on the side ipsilateral to the dermal symptom site, nail thickening/deformities and hair abnormalities (growth disorder of hair/alopecia on the affected side) concomitantly occur. In some patients, scoliosis or pes valgus is noted. On X ray, some patients show punctate ossification of the epiphysis of the limb on the affected side. Clinical symptoms derived from abnormalities in the affected-side heart, brain and kidney are sometimes observed.

Histopathological findings

Various reports on this issue have been published. At the site of ichthyosiform erythroderma, thickening of the stratum corneum and incomplete cornification are observed. Some patients show granular degeneration and others show slight bleb formation. Psoriasis-like thickening of the epidermis is also observed. Epidermal processes are elongated. The thickness of the abnormal cornification site (overcornification, incomplete cornification or mixed cornification) is similar to that of normal epidermis in some cases. In the corium, slight infiltration of cells is observed. Most patients show the infiltration of cells including monocytes, whereas some patients show that of eosinophils.

On electron microscopy, the following findings are noted: giant lipid droplets are observed in the cytoplasm of histiocytes around corium blood vessels. The keratin fibers of spinous stratum cells are thin and their count is decreased. Furthermore, a large number of vesicles are present. In the granular layer, the number of vesicles is increased. Although lamellar granules with a normal morphology are also present, there are a large number of vesicles, measuring approximately 200 nm in diameter, without a layer structure in the inner area. In keratinocytes, a large number of vesicular structures are also observed. Furthermore, such structures are present between keratinocytes.

Examination finding

X ray
Dysplasia of the long bone is one of the most important characteristics of CHILD syndrome. Its grade varies, from complete defects to shortening. A study reported assimilation of the vertebrae. Another study indicated a defect of the kidney on the affected side. Shortening of the long bone is observed in some

patients. According to a study, hepatomegaly and muscular hypoplasia were noted.

Electroencephalography
Electroencephalographic abnormalities are noted in some patients.

CT, MRI
Punctate ossification of the pelvic bone and ossification of the thyroid cartilage are observed. Some patients show hypoplasia of the brain. Hypoplasia and defects of the thyroid, adrenal glands, lungs and ovaries have been reported.

Echocardiography/cardiac catheterization
Congenital cardiac anomalies, such as ventricular and atrial septal defects, have been reported.

Diagnosis/differential diagnosis
Congenital hemidysplasia, ichthyosiform erythroderma or nevus and limb defects syndrome must be differentiated from X-linked dominant chondrodysplasia punctata. In patients with this disease, punctate ossification of the epiphysis is also observed, but ichthyosiform erythroderma is bilateral, and overcornification of the skin is noted as a linear or macular lesion along Blaschko's line. In schoolchildren, differential diagnoses are made based on atrophic changes of cornified lesions. In the presence of X-linked dominant chondrodysplasia punctata, shortening of the limbs is observed, but there are no defects. Furthermore, ocular lesions (cataract) are detected in some patients. In addition, CHILD syndrome must be differentiated from unilateral ichthyosis hystrix Curth–Macklin.

Treatment
A study reported that non-steroidal anti-inflammatory drugs were effective. Another study indicated that patients responded to 10% urea cream, retinoid therapy, and methotrexate therapy.

Course/prognosis
Anomalies of the main organs influence the prognosis. Some patients die before 1 year of age, whereas others survive for more than 20 years.

ICHTHYOSIS, BRITTLE HAIR, IMPAIRED INTELLIGENCE, DECREASED FERTILITY AND SHORT STATURE (OMIM NO. 601675)

Epidemiology
Ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature (IBIDS) is extremely rare. Only 15 patients were reported between 1968 and 1987.[30,31]

Etiology/pathological physiology
The form of inheritance of this disease is autosomal recessive.[31] This disease is classified into three types: trichothiodystrophy (TTD)/XP-D, in which excision-repair, complementing defective, in Chinese hamster, 2 (ERCC2)/xeroderma pigmentosum, complementation group D (XPD) gene mutations are detected; TTD/XP-B, in which ERCC3/XPB gene mutations are detected; and TTD-A. Both ERCC2/XPD and ERCC3/XPB are the subunits of a transcription factor for DNA repair, TFIIH. ERCC2/XPD has single-strand DNA-dependent ATPase and ATP-dependent 5′→3′ DNA helicase activities.

In most patients with IBIDS, ERCC2/XPD gene mutations have been detected, and ERCC3/XPB gene mutations have been identified in only a small number of patients.[31,32] In ERCC2/XPD molecules, many mutations, including G713R mutations, have been identified. In 1996, Takayama *et al.* identified R658C or R658H mutations in ERCC2/XPD molecules, and reported that these mutations were related to moderate photodermatosis. R722W mutations in ERCC2/XPD molecules were detected in IBIDS patients with severe photodermatosis. In 1997, Weeda *et al.* identified T119P mutations in ERCC3/XPB molecules. In other patients, L461V, the deletion of amino acid numbers 716–730, and A725P amino acid mutations were identified as mutations in ERCC2/XPD molecules. However, L461V has been detected not only in IBIDS patients but also in XPD ones. Recently, a type of IBIDS, TTD-A, was shown to be associated with a low level of TFIIH. A defect of a TFIIH-stabilizing substance may be involved in the etiology of TTD-A.

Clinical symptoms
Some patients were born as collodion babies (family of Weeda *et al.*). Their characteristic findings include a short stature. The subcutaneous fat level is also decreased, and their faces have a characteristic appearance (senile face). In addition, the ear cartilage level is decreased, systemic erythema is observed and brown polygonal scales are marked at the limb ends. This type of ichthyosis intermittently appears in some patients. Cornification of the palms and heels is present. Nail thickening is noted. Hair is short and fragile. The eyebrows are thin. A study reported normal teeth, whereas another study indicated that the incidence of caries was high. Hypogonadism is present, and cryptorchidism is observed in some patients. The testis size is smaller than in normal adults. Congenital bilateral cataract is noted in some patients. Photodermatosis at various grades is present. In some patients, asthma or otosclerosis is concomitantly present. Furthermore, infection frequently occurs. IBIDS does not induce skin cancer, differing from xeroderma pigmentosum. A study reported the concomitant development of microcephaly or deafness.

Histopathological findings
The histology of non-bleb-type congenital ichthyosiform erythroderma is observed.

Examination
The results of peripheral blood and liver function tests are normal. An intelligence test shows a reduction in IQ. There is a

decrease in the sulfur content of hair. Hair amino acid analysis must be performed to confirm a decrease in the cystein or proline residue. When patients' hair is examined under a light microscope, trichoschisis or pili torti is observed. On DNA repair or photodermatosis tests, abnormalities are noted. There are no orthopedic abnormalities.

Diagnosis/differential diagnosis

Ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature must be differentiated from non-bleb-type congenital ichthyosiform erythroderma, Netherton syndrome, SLS and Conradi–Hünermann–Happle syndrome. In patients with Netherton syndrome, ichthyosis linearis circumflexa is noted. Furthermore, most patients have atopic predispositions, such as hives and asthma. In those with SLS, hair and nails are normal. In those with X-linked dominant ichthyosis, ichthyosiform erythroderma-related exanthema shows a spiral distribution along Blaschko's line. Furthermore, cataract concomitantly develops.

Treatment

According to a study, the application of skin-softening drugs is effective. Neither retinoid therapy nor keratolytic drugs are effective. To control photodermatosis, sunscreen products should be used. To treat contracture of the fingers and toes, physical therapy should be performed.

Prognosis

Patients who died during childhood have been reported.

CONRADI–HÜNERMANN–HAPPLE SYNDROME (OMIM NO. 302960)

Epidemiology

Conradi–Hünermann–Happle syndrome is rare. Since Bloxosom and Johnston reported it in 1938, only 36 patients were reported globally before the report published by Happle in 1979.[33,34] All patients were female.

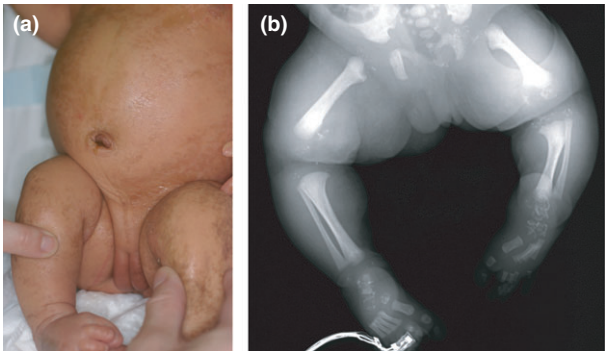

Figure 1. Conradi–Hünermann–Happle syndrome. (a) Linear or whorled atrophic and pigmentary skin, and striated hyperkeratosis. (b) Punctiform calcification of the bones and asymmetric shortening of the bone (courtesy of Professor Fukai, Osaka City University, Japan).

Etiology/pathological physiology

This disease exhibits X-linked dominant inheritance, and has been shown to be related to the mutation of a gene coding Δ8-Δ7 sterol isomerase, that is, emopamil-binding protein (EBP). EBP is an enzyme involved in the process of cholesterol synthesis. It acts downstream of NSDHL.

Clinical symptoms

This condition has four signs, consisting of ichthyosis, punctate cartilage aplasia, cataract and a short stature.[35] The skin shows symptoms of erythroderma early after birth. Scales are marked, and exanthema shows a spiral (mosaic-like) distribution along Blaschko's line (Fig. 1a). This type of exanthema related to ichthyosis gradually decreases within a few months after birth, leading to dermal atrophy, pigmentation and depigmentation. As asymmetrical shortening of the long bone occurs, kyphoscoliosis appears (Fig. 1b). Keratosis of the palms/heels and nail thickening are observed in some patients. Facial asymmetry and unilateral cataract are also noted. Alopecia of the scalp is observed.

Histopathological findings

At the site of ichthyosis, thickening of the epidermis and stratum corneum is observed. The granular layer is decreased. Partially, incomplete cornification is present. Atrophy of hair follicles and slight cell infiltration around corium blood vessels are noted. Calcium deposition in the epidermis and the presence of needle-like structures in granular layer cells have been reported.

Examination

X ray

Plain chest X-ray shows scoliosis.

Otorhinolaryngological examination

Patients with hearing impairment involving the high-frequency range have been reported.

Diagnosis/differential diagnosis

Conradi–Hünermann–Happle syndrome must be differentiated from non-bleb-type congenital ichthyosiform erythroderma, Netherton syndrome, SLS and IBIDS. A prenatal diagnosis can be made by measuring dihydroxyacetone phosphate acyltransferase activity. Ultrasonic diagnosis during pregnancy facilitates the detection of fetal skeletal abnormalities.

Treatment

A study indicated that phototherapy with ultraviolet (UV)-A/UV-B and topical steroid therapy reduced this disease. Skin-softening drugs are effective. The effects of retinoid therapy are unclear. To treat skeletal abnormalities, orthopedic treatment must be performed.

Prognosis

Unless marked scoliosis affects the heart/lung functions, the prognosis may be favorable.

DORFMAN–CHANARIN SYNDROME (OMIM NO. 275630)

Epidemiology
Dorfman–Chanarin syndrome is rare. There were only 18 case reports globally as of 1994.[36]

Etiology/pathological physiology
Dorfman–Chanarin syndrome exhibits autosomal recessive inheritance. This syndrome is characterized by lipid droplet in leukocytes. In 1976, Hays *et al.* found that the triglyceride level increased 20–70-fold above the normal value, as determined using thin-layer chromatography.[36,37] A recent study showed a marked reduction in the oxidation of intrinsic triglycerides, but there were no abnormalities in the lysozome level, suggesting that mitochondrial lipid oxidation is affected. Dorfman–Chanarin syndrome is caused by homozygous mutation in the comparative gene identification-58 (CGI58) gene.[36]

Clinical symptoms
Clinical symptoms of Dorfman–Chanarin syndrome resemble those of non-bleb-type congenital ichthyosiform erythroderma (patients are not collodion babies at the time of birth) (Fig. 2a, b). Pruritus is severe. There is a decrease in the sweat volume. The clinical symptoms include various symptoms related to liver dysfunction, muscular weakness, cataract, renal dysfunction, deafness, mental retardation, nervous diseases and a short stature.

Histopathological findings
At the site of ichthyosis, overcornification, thickening of the granular layer and epidermal thickening are observed. In basal layer cells, lipid droplets are detected. There is no incomplete cornification. On electron microscopy, abnormalities in lamellar granules are noted. In patients with Dorfman–Chanarin syndrome, there is no layer structure in lamellar granules. The cytoplasmic number of granules increases, leading to the formation of a cleft, with low electron density, between the stratum corneum and granules.

Examination
Liver dysfunction (increases in the levels of aspartate aminotransferase, alanine aminotransferase and γ-glutamyltransferase) is noted. On Pappenheim or oil red O staining, lipid droplets are observed in leukocytes (especially neutrophils) (Jordan abnormality) (Fig. 2c,d). The scale triglyceride level is increased.

Diagnosis/differential diagnosis
This disease must be differentiated from Refsum syndrome. In patients with Refsum syndrome, lipid droplets are present in the cytoplasm of epidermal basal cells, but not in other tissues. In those with Dorfman–Chanarin syndrome, cytoplasmic lipid droplets are observed in the skin, muscles, liver and polynuclear leukocytes (neutrophils, basophils and eosinophils).

Treatment
The application of skin-softening drugs and p.o. administration of retinoid are effective. A fat-restricted diet is not effective.

Course/prognosis
Despite lipid deposition in systemic tissues, the prognosis is favorable.

ICHTHYOSIS FOLLICULARIS WITH ALOPECIA AND PHOTOPHOBIA (OMIM NO. 308205)

Epidemiology
Ichthyosis follicularis with alopecia and photophobia (IFAP) is extremely rare. Since MacLeod described this disease in 1909, approximately 10 patients have been reported globally.[38–40]

Etiology/pathological physiology
X-linked recessive inheritance is suggested. IFAP is caused by mutation in the *MBTPS2* gene on chromosome Xp22. *MBTPS2*

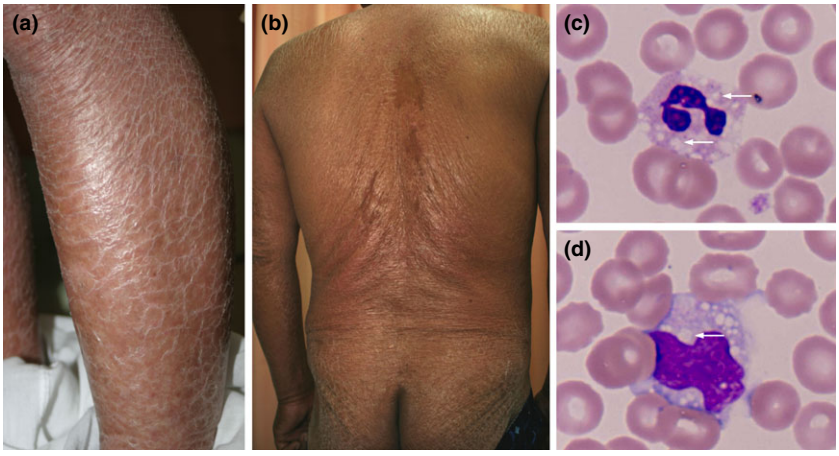

Figure 2. Dorfman–Chanarin syndrome. (a,b) Non-bullous congenital ichthyosiform erythroderma. (c,d) Fat-containing cytoplasmic vacuoles in the leukocytes (Jordans anomaly) (white arrows) (courtesy of Professor Sano, Kochi University, Japan).

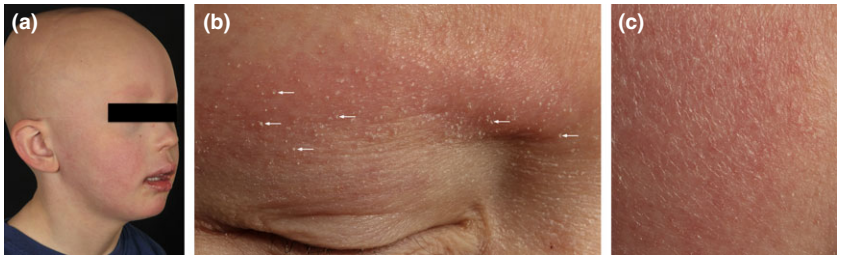

Figure 3. Ichthyosis follicularis, atrichia, and photophobia syndrome. (a) Complete baldness. (b) Follicular hyperkeratosis of the eyelid (white arrows). (c) Dry and mild erythematous skin with fine scaling (courtesy of Professor McGrath, King's College London, UK).

gene encodes membrane-bound transcription factor protease, site 2 (MBTPS2) protein.[38]

Clinical symptoms

A short stature and mental retardation are observed. Convulsion concomitantly occurs.[38–40] Alopecia totalis, hypohidrosis and photophobia are noted. Inguinal hernia and vertebral/renal abnormalities are present (Fig. 3a). The severity of ichthyosis is moderate (Fig. 3c). Cornified lesions are primarily observed in the gluteal region, femur and knees. In hair follicles, cornification is marked (Fig. 3b). Although erythroderma with inflammation is absent, some patients show erythema of the palms/heels. There is no cornification in the palms or heels. Defects of eyebrows and eyelashes are noted. Thickening of finger/toenails is observed. Some patients frequently develop hives, and others show infection-prone features.

Histopathological findings

Hyperkeratosis of the hair follicle infundibulum is observed. Atrophy of hair bulbs is noted, and cell infiltration is observed around them. The sweat glands are normal, but the sebaceous glands show atrophy. The stratum corneum of the interfollicular epidermis is thickened, showing the histology of overcornification. The granular layer is present.

Examination

Electroencephalographic abnormalities are detected in some patients. Ophthalmological examination reveals a decrease in lacrimation in some patients. A study indicated that the blood levels of IgG, IgM, IgA and IgE were increased.

Diagnosis/differential diagnosis

Ichthyosis follicularis with alopecia and photophobia must be differentiated from keratosis follicularis spinulosa decalvans (KFSD) (a portion of lichen spinulosus), Graham–Little syndrome, ulerythema ophryogenes and keratosis pilaris rubra atrophicans face. Cornification of the palms/heels is present in patients with KFSD, but not in those with IFAP. In those with ulerythema ophryogenes, there is no photophobia.

Treatment

Topical therapy with skin-softening and keratolytic drugs is performed. Their effects have been reported. A study indicated the efficacy of retinoid therapy.

Course/prognosis

The prognosis is favorable, but exanthema may persist over the lifetime.

HYSTRIX-LIKE ICHTHYOSIS WITH DEAFNESS (OMIM NO. 602540)

Definition/entity

In 1977, Schnyder[41] and Gulzow *et al.*[42] reported a patient with a marked overcornified plaque and deafness. Thereafter, solitary patients were reported by Badillet *et al.*[43] and Baden *et al.* Electron microscopic findings differ from those of other types of dyskeratosis. Currently, this is regarded as a disease. However, Nousari *et al.* reported a patient with KID syndrome and ichthyosis hystrix Curth–Macklin, and regarded hystrix-like ichthyosis with deafness (HID) as a phenotype of KID syndrome.

Epidemiology

This disease is extremely rare. Only a few patients have been reported globally.

Etiology/pathological physiology. Hystrix-like ichthyosis with deafness syndrome is caused by heterozygous mutation in the connexin-26 gene, *GJB2*.[45] The *GJB2* gene is located at human chromosome 13q12.11.

Clinical symptoms

Symptoms appear immediately after birth. Fine, white scales affect the whole body. Ichthyosiform erythroderma with hystrix-like cornification is observed. On the face, red keratotic papules are present. On the flexion side of the limbs, gray hyperkeratotic plaques are present. The skin is slightly red. There is a marked decrease in the sweat volume. Sensorineural hearing loss concomitantly develops. Bacterial/fungal infection may occur.

Histopathological findings

Thickening of the stratum corneum, papillomatosis and partial epidermal thickening are observed. Partially, incomplete cornification sites are present. Partial thickening of the granular layer is noted. Keratinocytes often show vacuolation. Around nuclei, a halo is present. In the cytoplasm, annular keratohyaline granules are present. They are called birds eyes. In the

corium, moderate cell infiltration is observed. On electron microscopy, there is a decrease in the number of intermediate filaments, and a large number of mucous granules are present in the cytoplasm. Granular contents are released to the intercellular space, being maintained there.

Examination

Audiography is performed to investigate the presence or absence of hearing disorder. There are no disease-specific abnormalities in blood laboratory data.

Diagnosis/differential diagnosis

The differential diagnosis of HID syndrome from KID syndrome is sometimes difficult. In patients with KID syndrome, dermal findings include papilloma-like hyperkeratosis. In these patients, corneal neovascularization is observed. They show normal findings on electron microscopy.

Treatment

A study reported that etretinate was effective.

Course/prognosis

The prognosis is favorable, but exanthema may persist over the lifetime.

CONCLUDING REMARKS

The recent understandings for multisystem ichthyosis syndromes are greatly expanding. Further basic and clinical research is mandatory to achieve new therapeutic options.

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